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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,451	DOW ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 55-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 55-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/23/04, 3/4/ 04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' preliminary amendment, which included cancellation of claims 2-55 and addition of new claims 55-62, filed on 1/23/2004 is made of record.

Claims 1 and 55-62 are now pending.

Information Disclosure Statement

References cited in the Information Disclosure Statements filed on 1/23/2004 3/4/2004, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 55-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being a dependent claim on a rejected claim and share the same indefiniteness .

1. Recitation of the term "prodrug" in the instant claims is deemed as indefinite. Prodrugs in general and as noted in specification, page 18, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various R groups include such groups, namely esters, alkoxycaronyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug group.

In addition, it is not clear whether compounds bearing these groups are excluded from being potential "prodrug". If compounds bearing these groups, which are likely to undergo in vivo transformation, is excluded then what is included in the definition of prodrug and where on the compound of formula I, these groups are placed, is not clear.

2. Recitation of the term "isomer" in the instant claims renders ambiguity to these claims, as it is not clear what isomer is claimed. Note isomer can be optical, geometrical, positional isomer etc. Specification has no definition of the term and hence it is not clear what is being claimed. The scope of the claim is vague and unclear. Given the structural variant possible for the genus, it is not possible to know what is included and what is not. The metes and bounds of the claims remain unknown. A proper search is therefore not possible with additional restrictions.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 55-62 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds positively recited in these claims does not reasonably provide enablement for "isomer" embraced by the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in

scope with these claims. Following reasons apply. Any claim not specifically rejected is rejected as being a dependent claim on a rejected claim and has the same limitation.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to isomer, which as recited reads on any or all isomers including those yet to be discovered as isomer of the instant compound, for which there is no enabling disclosure. Specification is not adequately enabled as to what these isomers are and how to make isomer of compound of formula (I).

Prior art search in t e related area does not suggest any isomer of instant class of compounds. Specification offers no teachings or suggestion what the structural make-up o f the isomer of compound of formula I and to how to make. Furthermore, there is no teaching or suggestion that the intended isomer would have the same utility.

2. The predictability or lack thereof in the art:

Hence the product and process as applied to the above-mentioned isomer compounds claimed by the applicant is not an art-recognized and hence there

should be adequate enabling disclosure in the specification with working example(s) and testing as to the utility of the isomer

4. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as what to make and test as isomer.

5. The presence or absence of working examples:

Examples shown in the specification are limited to compound of formula I, which is positively recited and claimed, and there are no representative examples showing isomeric compounds and the viability of the process and utility. . Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

6. The breadth of the claims:

Specification has no support, as noted above, for all isomeric compounds generically embraced in the claim language and support for process of making that they would lead to desired compound of formula I with said utility.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of

experimentation, there is no guarantee that one would get the product of desired structure, namely isomeric compound of formula I embraced in the instant claims in view of the prior art teachings.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc. have been demonstrated to be sufficiently lacking in the case for the instant claims.

Claims 1 and 55-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must

itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The general direction concerning the prodrugs is found in page 18, paragraph 1

c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. l) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally

considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. US 3,905,971.

Miller et al. teaches several similar 2-phenyl-1,2,4-triazidinone compounds, which include compounds, claimed herein for the use as coccidiosis agents. See general

formula shown on col. 1, lines 45-60 and note the definition of R_2, R_3, R_4, R_5, R_6 and R_{10} groups shown on col. 1 and col. 2. Note when R_4 is formula II or III (i.e. X-phenyl group) as shown on col. 2, line 10-20, the compound of general formula of Miller et al. include compounds claimed herein. Note loweralkyl is a s defined therein is C_1-C_6 alkyl. See col. 3-6 for details of the invention and examples on col. 10-18 for compounds made and tested. Particularly, see tables on col. 11-12, and col. 13-16 for compounds. Especially note Miller et al teaches dialkyl, dialkyloxy and alyl-alkyloxy substituents in the phenyl. See col. 13, lines 59-64 , col.14, lines 8-9 and col. 26, line 3.

Miller et al. differs in not teaching compounds bearing an alkoxy and C_5 or C_8 alkyl in the phenyl ring but teaches 4-OC_4H_9 and C_2H_5 as seen in line 8-9 of col.26.

However, Miller et al. teaches the equivalency of exemplified substituted 1,2,4-triazinediione shown in examples and the tables stated above with 1,2,4-triazinedione with variously substituted in both aryl rings and the triazine claimed in the definition of compound of general formula. See cols. 1 and col. 2, especially see the definitions of the definition of X' X", Y', Y", R_2, R_3, R_4, R_5, R_6 , R_{10}, R_{11} and R_{12} groups .Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made would have been to make compounds variously substituted triazine and aryl rings including compounds bearing an alkoxy and C_5 or C_8 alkyl in the phenyl ring as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 55-59 and 61 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,787,652. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims is an obvious variant of the subject matter taught in the claims of US 6,787,652. Note when R^5 is hydroxyl or methoxy, and R^4 is $C(R^{14})(R^{15})(R^{16})$, all other variable R groups being same as defined in the instant claims, the compounds, taught by US 6,787,652 overlap with the instant claims 1, 55-59 and 61.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to

reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Venkataraman Balasubramanian

Venkataraman Balasubramanian

10/28/2004